

VIA EFS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: §
Jose Vicente Murillo Garrido *et al.* §
§
Conf. No.: 3364 § Group Art Unit: 1612
§
Appln. No.: 10/764,915 § Examiner: Sabiha Naim Qazi
§
Filing Date: January 26, 2004 § Attorney Docket No.: **9256-20US**
§ (003/PCT/02-V)
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Title: STEREOSELECTIVE PROCESS FOR THE PRODUCTION OF 6ALPHA-FLUORPREGNANES AND INTERMEDIATES

RESPONSE TO RESTRICTION AND ELECTION OF SPECIES REQUIREMENTS

This is in response to the Office Action dated April 2, 2008, (Paper No. 20080329). This response is being timely submitted in view of the submission herewith of a Petition for Extension of Time (three months) to and including August 4, 2008 (August 2, 2008 being a Saturday), including authorization to charge the extension fee.

The Office Action relates only to restriction and election of species requirements. The Examiner has identified nine groups of inventions, as follows:

- I. Claims 15-25, drawn to steroidal compounds of formula IV when C represents 1st structure in line 8 on page 30 and D ring represents any one structure of D of claim 15;
- II. Claims 15-25, drawn to steroidal compounds of formula IV when represents 2nd structure in line 8 on page 30 D ring represents any one structure of D of claim 15;
- III. Claims 15-25, drawn to steroidal compounds of formula IV when C represents 3rd structure in line 8 on page 30 D ring represents any one structure of D of claim 15;
- IV. Claims 15-25, drawn to steroidal compounds of formula IV when C represents 4th structure in line 8 one page 30 D ring represents any one structure of D of claim 15;

- V. Claims 6-34 drawn to process of making the compounds of formula IV (one process of each group I-IV will be joined with the elected group of compounds);
- VI. Claims 1-14 and 35-38 are drawn to process of making the compounds of formula (I) when C represents 1st structure and D ring represents any one structure of D;
- VII. Claims 1-14 and 35-38 are drawn to process of making the compounds of formula (I) when C represents 2nd structure and D ring represents any one structure of D;
- VIII. Claims 1-14 and 35-38 are drawn to process of making the compounds of formula (I) when C represents 3rd structure and D ring represents any one structure of D; and
- IX. Claims 1-14 and 35-38 are drawn to process of making the compounds of formula (I) when C represents 4th structure and D ring represents any one structure of D.

The Examiner has required an election of one single group from the above 9 groups.

The Examiner has also required an election of a single species from the elected group.

The Examiner indicates that claims 1, 15 and 26 are generic to patentably distinct species and that the species are independent or distinct because as disclosed the different species have mutually exclusive characteristics and are not obvious variants of each other based on the current record. It is not clear from the Detailed Action, what are the distinct species the Examiner refers to. Since the Examiner has explicitly required the Applicants to elect one D ring from the elected group, Applicants consider the election of species requirement is directed at the election of one D ring from the four D rings recited in the claims.

Applicants respectfully traverse the restriction requirement and the election of species requirement for the following reasons.

The present application relates in general to a process for producing 6 α -fluorpregnanes of formula (I), which are useful for activation of steroids, by introducing fluorine at position 6 of the steroids, with high yields and maximum stereoselectivity. Claims 1-14 (Groups VI-IX) are directed at a process of making 6 α -fluorpregnanes from silylated intermediates of formula (IV). Claims 15-25 (Groups I-IV) and claims 26-34 (Group V) are drawn to the silylated intermediates and a process of making the silylated intermediates, respectively. Claims 35-38 (Groups VI-IX) are drawn to a process of making 6 α -fluorpregnanes, which includes both the process of making

the silylated intermediates and the process of making 6α -fluorpregnanes from the silylated intermediates.

Applicants respectfully submit that the restriction and election of species requirements between silylated intermediates of Groups I-IV based on the structures of the C and D rings are improper, because the silylated intermediates have a common property and the structures of the C and D rings do not affect the common property. The common property among silylated intermediates of Groups I-IV is that they all serve as intermediates for making 6α -fluorpregnanes of formula (I) by reacting with an N-fluorosulfonimide- or an N-fluorosulfonamide type fluorinating agent, which leads to the stereoselective introduction of fluorine at position 6 of the 6α -fluor pregnanes, with a very high $6\alpha/6\beta$ fluorine epimeric ration and with a very low production of impurities (paragraph [0020], right before Brief Summary of the Invention). The inventors discovered that the combination of silyl derivatives and the fluorine reagent derived from sulfonamide and sulfonamide is necessary for making fluorinated 6α derivatives diastereoselectively. Other combinations, such as enol ethers and fluorine reagents, or silyl derivatives and selectfluor or other fluorinating agents, do not work as can be seen in the reference examples of the present application.

According to the disclosure of the present application, the diastereoselectivity may only be obtained by using a stable silyl enol ether, such as that in the silyl derivatives of formula (IV), which withstands the fluorination conditions without breaking until the fluorine atom has been introduced, and by using a gentle enough fluorine reagent, such as the N-fluorosulfonimide- or N-fluorosulfonamide type fluorinating agent, so that the silyl derivative does not break before introducing the fluorine. As described in the background of the present application, the relevant prior art references are those relating to introducing a fluorine atom at position 6α in steroids with a basic “pregnane” structure with the common “4-ene” or “1,4-diene” and “3,20-dione” structures. The rest of the structures in formula (IV), including the C and D-rings, which takes into account of possible pharmaceutically useful structures, does not materially affect the diastereoselectivity of the silyl derivatives.

Therefore, Applicants respectfully submit that the silyl derivatives of Groups I-IV are related because they share the above mentioned common property, and the search and examination of the silyl derivatives together should not impose significant burden on the Examiner.

Applicants respectfully submit that the restriction and election of species requirements between the silylated intermediates of Groups I-IV and the process of making the silylated intermediates of Group V are improper, because the Examiner has failed to show that the silylated intermediates of Groups I-IV can be made by another process that is materially different from that of Group V. The Examiner indicates that inventions in Groups V and I to IV are related as process of making and product made, and that they are distinct because the product as claimed can be made by another and materially different process. However, the Examiner has not provided any information about the other materially different process.

Contrary to the Examiner's assertion, Applicants believe that the silylated intermediates of Groups I-IV could only be practically synthesized by the method of Group V. Applicants respectfully submit that the silyl derivatives had not been described until the time the present application was filed. Therefore, other means of making them had not been previously described either. Applicants further submit that it is difficult to make the silyl derivatives by synthesis means other than those described in the specification, and that even if other means of synthesis did exist, they would not be easy to carry out from a practical or industrial point of view. Thus, inventions of Groups I-IV and V are related. In addition, in order to search and examine the process of Group V, the Examiner would have to search and examine the product of Groups I-IV. Thus, there should not be undue burden for the examiner to search and examine the products of Groups I-IV and the processes of Group V together.

Applicants respectfully submit that the restriction and election of species requirements between the silylated intermediates of Groups I-IV and the process of making 6α -fluor pregnanes of Groups VI-IX are improper, because the silylated intermediates are necessary and indispensable for carrying out the process of making 6α -fluor pregnanes. The process recited in claims 1-14 comprises reacting the silylated intermediates with an N-fluorosulfonimide- or an N-

fluorosulfonamide type fluorinating agent to obtain the 6α -fluor pregnanes. The process recited in claims 35-38 comprises (a) obtaining the silylated intermediates by reacting a pregnane derivative of formula (II) with a (trisubstituted)silyl trifluoromethanesulfonate of formula (III); and (b) reacting the silylated intermediates with an N-fluorosulfonimide- or an N-fluorosulfonamide type fluorinating agent to obtain the 6α -fluor pregnanes. Thus, the processes of claims 1-14 and 35-38 (Groups VI-IX) have the following two essential elements: (a) the silyl derivatives of formula (IV), and (b) the N-fluorosulfonimide- or N-fluorosulfonamide type fluorinating agent.

In order to search and examine the process of Groups VI-IX, the Examiner would have to search and examine the silyl derivatives of Groups I-IV. In addition, Applicants were not aware of any use of the silyl derivatives beyond that of facilitating the introduction of a halogen atom, fluorine being the only halogen of commercial and pharmacological interest, at position 6 of the steroids with high yields and maximum stereoselectivity, at the time the application was filed. Accordingly, the silyl derivatives of Groups I-IV and the process of Groups VI-IX are related. The search and examination of these inventions together should not impose extra burden to the Examiner.

Applicants respectfully submit that the restriction and election of species requirements between the processes of Groups V and VI to IX are improper, because the processes are not mutually exclusive. The Examiner states that inventions of Groups V and VI to IX are directed to processes of making, and that they are distinct because they do not overlap in scope, i.e., they are mutually exclusive, and that there is nothing of record to show them to be obvious variants. Applicants respectfully disagree. The processes of Groups VI-IX (claims 1-14 and 35-38) are related and not mutually exclusive, because the process of claims 35-38 includes the process of claims 1-14 as its step (b). The process of claims 35-38 (Group VI-IX) and the process of Group V are related and not mutually exclusive, because the process of claims 35-38 includes the process of Group V as its step (a). The process of claims 1-14 (Group VI-IX) and the process of Group V are related, because the process of claims 1-14 involves silylated intermediates as an essential element and the process of Group V is directed at making the silylated intermediates.

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Accordingly, the processes of Groups V and VI to IX are related. The search and examination of these processes together should not add extra burden to the Examiner.

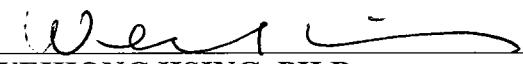
Accordingly, Applicants respectfully urge the Examiner to reconsider and withdraw the restriction and election of species requirements.

Pursuant to 37 C.F.R. § 1.143, in the event that the restriction requirement is not withdrawn, Applicants hereby provisionally elect, with the foregoing traverse, the invention of Group VII, claims 1-14 and 35-38 where the C ring represents the second structure (epoxide), for initial examination in this application. In the even that the election of species requirement is not withdrawn, Applicants hereby provisionally elect within the elected Group VII, with the foregoing traverse, the species where the D ring corresponds to the second structure with group R₄ in position 16 and group OP' in position 17.

Early substantive examination and a Notice of Allowance with respect to all claims are respectfully solicited.

Respectfully submitted,

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